Immune Checkpoint Inhibitor–Associated Diabetes: A Single-Institution Experience

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OBJECTIVE

To characterize immune checkpoint inhibitor–associated diabetes mellitus (ICI-DM) in a single-institution case series.

RESEARCH DESIGN AND METHODS

Retrospective chart review of 18 patients with new-onset ICI-DM following anti–programmed cell death protein 1 (PD-1)/anti–programmed cell death protein ligand 1 (PD-L1) therapy for advanced carcinomas.

RESULTS

Of 18 patients, 9 had diabetic ketoacidosis (median glucose 27.92 mmol/L; median glucose before presentation 6.35 mmol/L). Median C-peptide at ICI-DM diagnosis was low, and it declined during follow-up. Median anti-PD-1/anti-PD-L1 duration before ICI-DM was 3.65 months (range 0.56–12.23 months). Time to ICI-DM onset was a median 1.4 months/3 ICI cycles and 6 months/10 cycles in those patients who were positive and negative for GAD65 autoantibodies, respectively. Time to ICI-DM onset was a median 2.5 months/3 ICI cycles and 4.8 months/8 cycles after anti-PD-L1 or anti-PD-1 therapy, respectively. Significant pancreatic atrophy was seen radiographically.

CONCLUSIONS

ICI-DM presents abruptly, appears irreversible, is characterized by pancreatic atrophy, and may occur both earlier following PD-L1 blockade compared with PD-1 inhibition and in those who have positive GAD65 autoantibodies.

Immune checkpoint inhibitors (ICIs) profoundly affect oncologic care by suppressing physiologic blocks on immune responses, resulting in immune-mediated antitumor activity. ICIs include agents that block cytotoxic T-cell–associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed cell death protein ligand 1 (PD-L1). Autoimmune toxicities following ICI use have distinct clinical presentations (1,2). Anti-PD-1/PD-L1 agents are associated with new-onset insulin-dependent diabetes mellitus (IDDM) presenting as diabetic ketoacidosis (DKA) or severe hyperglycemia. ICI-associated IDDM (ICI-DM) appears to occur more abruptly compared with type 1 diabetes (T1D) (3–10). We report the largest single-institution case series of ICI-DM to date, including characterization of ICI-DM-associated pancreatic atrophy on imaging.

RESEARCH DESIGN AND METHODS

Upon Memorial Sloan Kettering Cancer Center institutional review board approval, records of patients treated with anti-PD-1/PD-L1 agents and developed new-onset

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NOVEL COMMUNICATIONS IN DIABETES

IDDM from May 2015 to May 2018 were retrospectively reviewed. Patients who developed new-onset hyperglycemia (random glucose >7.0 mmol/L) requiring insulin, DKA, or new-onset insulinopenia based on low random C-peptide levels (<0.26 nmol/L) were included. Descriptive patient data and laboratory studies, including random blood glucose values and associated clinical symptoms, were collected. Those with prior history of diet-controlled type 2 diabetes (T2D) were allowed in the study. Pancreatic parenchymal volumes were quantified. A single board-certified radiologist evaluated images to derive volumetric pancreatic parenchyma estimates:

$$\textit{Head volume} = \left(\frac{4}{3}\pi\right)\left(\frac{\text{anteroposterior diameter}}{2}\right)\left(\frac{\text{transverse diameter}}{2}\right)\left(\frac{\text{craniocaudad diameter}}{2}\right),$$

$$\text{based on ellipsoid volume} = \left(\frac{4}{3}\pi\right)(A)(B)(C), \text{where } A, B, C = \text{radius in each dimension}$$

$$\textit{Body to tail volume} = \pi\left(\frac{\text{average of 2 measurements for body to tail diameters}}{2}\right)^2(\text{body to tail length}),$$

$$\text{based on cylinder volume} = \pi\ (\text{radius})^2\ (\text{height of cylinder})$$

Baseline and last follow-up pancreatic volumes were derived from three-dimensional imaging available ~4–24 months before and 4–24 months following ICI-DM diagnosis, respectively. Volume changes around ICI-DM diagnosis, referred to as *pre-DM* and *post-DM* pancreatic volumes, were assessed by available scans 3 months before and after IDDM, respectively. Two-tailed Wilcoxon rank-sum testing compared patient characteristics. Overall survival was estimated using Kaplan-Meier methodology. Analyses were performed in R version 3.4.2.

RESULTS

A total of 18 patients met the study criteria (10 men and 8 women). Median age at ICI-DM diagnosis was 63.5 years (range 27–78 years). Of the 18 patients, 5 had prior prediabetes; 1 had prior diet-controlled T2D; 7 had a family history of T2D; and 1 had a family history of T1D. The most common primary cancer was melanoma ($n = 5$). All patients had stage 3/4 cancer, and all were treated with other cancer-treatment modalities (Supplementary Table 1). There were 16 patients who had disease progression or recurrence after prior treatments; 12 received anti-PD-1 therapy; 5 received anti-PD-L1 therapy; and 1 received anti-PD-1 and anti-PD-L1 agents at different times. Nine patients received CTLA-4 and PD-1/PD-L1 blockade (Supplementary Table 2). The most common presenting symptoms of ICI-DM were polyuria/polydipsia ($n = 9$); fatigue or generalized weakness ($n = 9$); abdominal pain, nausea, or vomiting ($n = 5$); or blurry vision ($n = 4$). Nine patients presented with DKA, and nine presented with hyperglycemia without DKA. Median initial glucose was 27.92 mmol/L (range 18.59–46.9 mmol/L). Median glucose before ICI-DM presentation was 6.35 mmol/L (range 4.38–14.49 mmol/L), collected a median of 16 days before ICI-DM (range 11–51 days). Median HbA_{1c} at ICI-DM diagnosis was 7.25% (56 mmol/mol), ranging from 5.8% to 9.5% (40–80 mmol/mol). Median fructosamine at ICI-DM diagnosis was 337.5 μmol/L (range 283–520 μmol/L) in six patients. Median random C-peptide at ICI-DM diagnosis was 0.07 nmol/L (range <0.01–0.55 nmol/L) (Supplementary Table 3). Of the 18 patients, 11 trended toward or had undetectable C-peptide levels (Supplementary Fig. 1); 3/10 patients had elevated amylase levels at ICI-DM diagnosis; and 4/10 had elevated lipase levels. Glucagon levels evaluated in six patients were within normal range or above. There were 5 of 12 patients who were positive for GAD65 autoantibodies. HLA class I bias was not observed (Supplementary Table 4).

Pancreatic imaging was analyzed in 18/18 patients. Significant pancreatic atrophy was seen following ICI-DM without clinical pancreatic exocrine insufficiency (Fig. 1) (Supplementary Table 5). There was no increase in imaging rates of pancreatitis/fat stranding within the pancreas parenchyma relative to ICI-DM. Median anti-PD-1/PD-L1 treatment duration before ICI-DM presentation was 3.65 months (range 0.56–12.23 months). ICI dose exposures before ICI-DM diagnosis varied widely (Supplementary Table 6). Of 18 patients, 8 received steroids for other indications; only 5 received steroids within 90 days, and 2 received them within 7 days of ICI-DM diagnosis (Supplementary Table 7).

All patients were treated with insulin and subsequently required basal and bolus regimens. After 3–6 months of the ICI-DM diagnosis, the required median insulin total daily dose was 0.49 units/kg (range 0.2–1.03 units/kg). There were 13 of 18 patients who had follow-up HbA_{1c} levels available 3 months to 2 years after diagnosis with varied diabetes control (7.5% [58 mmol/mol], range 6.1–9.2% [43–77 mmol/mol]) (Supplementary Fig. 2). Median follow-up of survivors after ICI-DM onset, since cancer diagnosis, and since anti-PD-1/PD-L1 therapy initiation was 19.2 months (range 0.19–29.7 months), 65.1 months (range 22.6–154.8 months), and 22.6 months (range 0.9–33.4 months), respectively. Four patients had complete response to ICI therapy. Disease progression occurred in 10 of 18 patients (Supplementary Table 8). At the end of follow-up, four patients died. Four experienced other endocrine adverse events attributed to immunotherapy: adrenal insufficiency secondary to hypophysitis ($n = 1$) and primary hypothyroidism ($n = 3$). Other ICI-related adverse events included gastrointestinal toxicity ($n = 4$), hepatotoxicity ($n = 6$), and dermatologic toxicity ($n = 8$) (Supplementary Table 9 and Supplementary Fig. 3).

CONCLUSIONS

ICI improves survival by activating T-cells to restore antitumor immunity. However, normal tissues may be affected, leading to immune-related adverse events. ICI-DM presents with acute marked hyperglycemia or life-threatening DKA. The most recent random blood glucose levels measured within weeks before ICI-DM were predominantly normal or only mildly elevated, confirming acute hyperglycemia. Median HbA_{1c} and fructosamine levels were also consistent with acute marked hyperglycemia versus a long-term process over months preceding testing.

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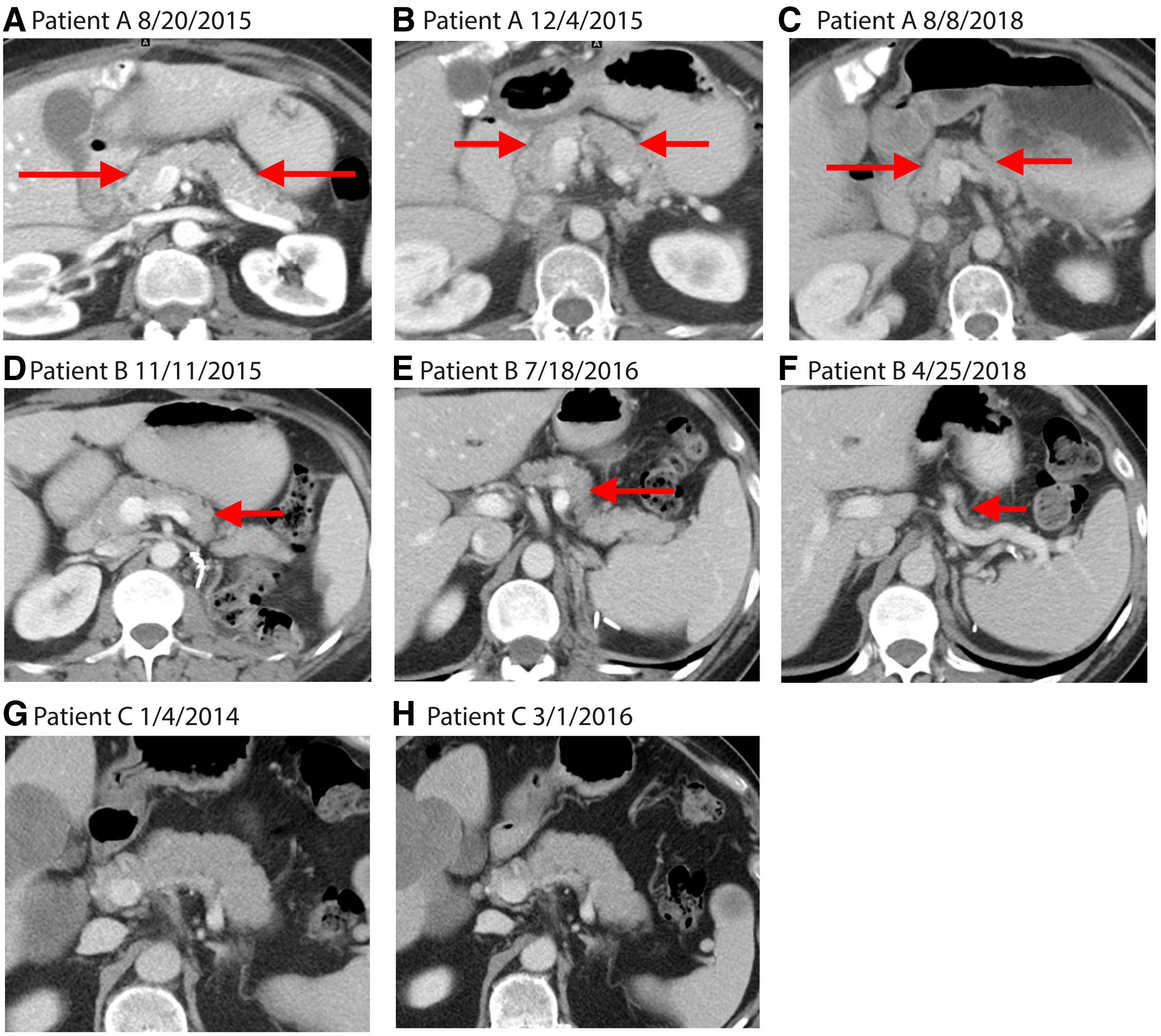

Figure 1—Computed tomography (CT) images of baseline and post-IDDM pancreas. On the basis of data from 18/18 patients, at baseline, before ICI-DM diagnosis, median pancreas volume was 76.63 cm^3 with a mean $\pm$ SD of 90.20 $\pm$ 33.4 cm^3, and pre-ICI-DM pancreas volumes were similar to baseline volumes. Immediately (approximately $\leq$3 months) after the IDDM diagnosis, median pancreas volume significantly declined to 63.65 cm^3 ($P < 0.001$), with a mean $\pm$ SD of 73.87 $\pm$ 34.9 cm^3. Pancreatic atrophy continued at the last available follow-up abdominal image, with a 53.92 cm^3 median pancreas volume ($P < 0.001$) and a mean $\pm$ SD of 59.90 $\pm$ 24.7 cm^3. Pancreas volume declined by a median 16% (interquartile range 10–25%) after the IDDM diagnosis and 31% (interquartile range 27–40%) at the last available follow-up image relative to baseline. The same radiologist also reviewed 10 sequential patients who presented without diabetes who had received anti-PD-1/anti-PD-L1 therapy. Pancreatic atrophy was not seen in any of these patients during ICI therapy. Patient A was a 58-year-old female treated with combination anti-CTLA-4 and anti-PD-1 therapy for stage 4 melanoma. *A*: Pretreatment CT scan demonstrates no evidence of pancreatic atrophy (arrows). *B*: Posttreatment scan 2 months after IDDM diagnosis again demonstrates no pancreatic atrophy (arrows). *C*: The last follow-up scan 3 years after ICI therapy demonstrates a significant decrease in pancreatic size (arrows) consistent with atrophy. Patient B was a 52-year-old male with metastatic renal clear cell carcinoma who had received anti-PD-1 therapy. *D*: Baseline scan prior to ICI therapy with normal-sized pancreas. *E*: Follow-up scan after ICI therapy at the time of IDDM diagnosis. The arrow demonstrates no evidence of pancreatic body atrophy. *F*: The last available follow-up CT 2 years after ICI therapy demonstrates the development of marked atrophy of the pancreatic body (arrow). Patient C was a 59-year-old male treated with anti-PD-1 therapy for metastatic melanoma who did not develop diabetes following therapy. *G*: A baseline scan prior to ICI therapy demonstrates a normal-sized pancreas. *H*: The last available follow-up CT 2 years after ICI therapy demonstrates no change in the size of pancreas since baseline.

Anti-PD-1/PD-L1 duration before ICI-DM onset ranged from ~2 weeks to 1 year and from 1 to 23 ICI cycles. All random C-peptide levels were low, with most becoming undetectable during follow-up, supporting β-cell destruction as being progressive and irreversible. Normal or elevated glucagon levels in our cohort may indicate pancreatic α-cell preservation. Median total daily dose of insulin was consistent with an insulin-sensitive phenotype as in T1D. Patients with ICI-DM are typically middle-aged or older adults who suddenly acquire this life-changing diagnosis.

We estimate the incidence of ICI-DM to be 0.37% based on the number who received anti-PD-1/PD-L1 therapy at Memorial Sloan Kettering Cancer Center during the study, in comparison with previously reported rates of 0.2–1.27% (1,10). Exploring factors that predispose patients to ICI-DM development, such as HLA-DR4, may help determine at-risk patients (7). Although our sample size was not large enough statistically, time to ICI-DM onset may be shorter in those patients who are positive for GAD65 autoantibodies, as median time to ICI-DM was 1.4 months/3 cycles versus 6 months/10 cycles in GAD-negative patients (Supplementary Table 8). This has been hypothesized by others as well (8,9,11).

The accelerated manifestation of ICI-DM is reflected by volume loss of previously normal pancreatic parenchyma, and it has also been described in non-ICI T1D (12–14). Median pancreas volume declined significantly from baseline before ICI-DM diagnosis to after ICI-DM diagnosis (median −16%), with continued significant decline at long-term follow-up (median −31%).

Although our series lacks sufficient power to detect significant subgroup differences, we recognize novel trends warranting further investigation. It is possible that time to IDDM is shorter in the anti-PD-L1 group (median 2.5 months/3 cycles) compared with anti-PD-1 group (median 4.8 months/8 cycles) (Supplementary Table 10). There were no apparent time to IDDM differences between groups receiving combination ICI therapy versus monotherapy (Supplementary Table 9). Lastly, autoimmune toxicity from ICI may be associated with improved cancer-specific mortality, as an overly robust immune system could lead to increased antitumor efficacy. Future evaluation of this relationship between ICI-DM and antitumor efficacy would be of great interest (15). As immunomodulatory therapies become prevalent, ICI-DM cases will increase. Understanding the novel presentation and natural history of ICI-DM, given its potentially life-threatening nature, is critical.

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